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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,549	12/22/2000	Santi Tofani	088.000426	3360

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,549	TOFANI, SANTI	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-67 and 69-76* is/are pending in the application.

4a) Of the above claim(s) *21-60,69,71,73 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-68,70,72,74 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 7/14/04 has been entered.

Claims 21-67 and 69-76 are pending in the present application.

This application contains claims 21-60, 69, 71, 73 and 75, drawn to an invention nonelected with traverse in the amendment filed on 10/29/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Accordingly, amended claims 61-68, 70, 72, 74 and 76 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-68, 70, 72, 74 and 76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make** and/or **use** the invention. ***This is a modified rejection necessitated by Applicant's amendment.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction

or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are directed to a method of using SELF [static magnetic (S) and extremely low frequency (ELF)] non-thermal fields for modification of a p53 gene, comprising applying said SELF non-termal fields to said p53 gene to be modified, wherein said SELF non-thermal fields have intensity in the range between 1 and 100 mT.

The specification teaches by exemplification showing that by applying SELF magnetic fields, apoptosis is induced in cultured human colon adenocarcinoma WiDr cells and human breast cancer MCF-7 cells, but not in normal human lung MRC-5 fibroblasts, with significant apoptosis effect was observed at the field intensity of 2 mT. However, the induced apoptosis does not depend upon SELF field frequency. Applicant further demonstrates that SELF fields have an inhibitory tumor growth effect in an experimental model of nude mice inoculated subcutaneously with human colon adenocarcinoma WiDr cells, as well as a decreased in p53 gene expression in exposed mice tumors. The above evidence has been noted and considered. However, the instant specification is not enabled for the presently claimed invention for the following reasons.

(1) The breadth of the claims. The claims are directed to a method of using SELF non-thermal fields for modifying (e.g., deletion, insertion, substitution at one

or more sites) any p53 gene (normal and/or mutant), wherein said SELF non-thermal fields have intensity in the range between 1 and 100 mT.

(2) The state and the unpredictability of the prior art. At the effective filing date of the present application (6/24/1998), nothing was known in the prior art on how to use methods of SELF non-thermal fields for the modification of any gene, let alone the modification of a normal and/or mutant p53 gene by SELF non-thermal fields having intensity in the range between 1 and 100 mT as evidenced by the teachings of Canedo et al. (U.S. Patent No. 5,752,911), Blackman et al. (U.S. Patent No. 5,919,679) and Montone L.J. (US Patent No. 5,156,587; IDS). Additionally, Blackman et al. stated "The results of a number of studies suggest that low intensity and low-frequency electric and magnetic fields may influence physiological processes in biological systems. However, most theoretical models developed to date have been unable to establish a predictive association between low-intensity field exposure and biological results" (col. 2, lines 14-19), and "A variety of theoretical models have been developed to describe the interaction of different combinations of static (DC) and extremely-low-frequency time-varying (AC) magnetic fields with living systems.....Most of the above-described models are largely descriptive, without being predictive" (col. 2, lines 45-55)

(3) The amount of direction or guidance provided. Apart from the exemplification showing that SELF non-thermal fields have an inhibitory tumor growth effect in an experimental model of nude mice inoculated subcutaneously with human colon adenocarcinoma WiDr cells, as well as a decrease in p53 gene expression in exposed mice tumors, the instant specification fails to provide sufficient guidance for a

skilled artisan on **how to use methods of SELF non-thermal fields** to modify any p53 gene, including any mutant p53 gene present in cancer cells. There is no evidence provided by the present application demonstrating that the mutant p53 gene in tumor cells exposed to SELF non-thermal fields is modified in any manner (e.g., deletion, insertion, substitution at one or more sites of the gene), let alone for the modification of normal p53 gene in normal cells. It is further noted that the specification teaches specifically that SELF non-thermal fields have no apparent toxicity effect or apoptotic effect on non-tumor cells in both *in vitro* and *in vivo*. The decrease in the level of p53 antigen that is detected by the immunohistochemical approach in tumor cells exposed to SELF non-thermal fields is not deemed to correlate with any modification of the mutant p53 gene present in tumor cells, let alone for normal p53 gene. This is because the decrease level of a p53 expression can be caused by a host of factors (e.g., transcriptional initiation, elongation, mRNA stability) that have nothing to do with the modification of the p53 gene. For example, the observed lower p53 expression level in cancer cells exposed to SELF non-thermal fields is apparently caused by an enhanced apoptotic rate and/or toxicity in the treated cancer cells (see Tables 3 & 4 for a significantly higher apoptosis, and lower proliferative index and mitosis in treated cancer cells), and not by the modification in the mutant p53 gene.

Furthermore, it is noted that enablement requires the specification to teach how to **make and/or use** the claimed invention. The instant specification also fails to provide sufficient guidance for a skilled artisan on how to use any p53 gene that is modified by SELF non-thermal fields in the method as claimed. Based on the present

disclosure, it is unclear what is the purpose for modifying any p53 gene. Since the prior art at the effective filing date of the present application does not provide any guidance on this matter, it is incumbent upon the present application to do so. As noted previously, the interaction of different combinations of static and extremely low frequency time varying magnetic fields with living systems in various theoretical models is largely descriptive, without being predictive (Blackman et al., U.S. Patent No. 5,919,679), then how could one use SELF non-thermal fields to modify any p53 gene with any degree of predictability to attain any beneficial or desirable effects or results in the method as claimed?

In light of the totality of the prior art at the effective filing date of the present application, and given the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan on how to make and use the method as claimed.

(4) Working examples. There is an absence of an example showing how to use SELF non-thermal fields for modification of any p53 gene in the method as claimed.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability and the state of the art on the make and use SELF non-thermal fields for any biotechnological gene modification, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the presently claimed invention.

Response to Arguments

Applicant's arguments related in part to the above rejections in the Amendment filed on 7/14/04 (pages 12-15) have been fully considered, but they are respectfully found to be unpersuasive.

Applicant presented the papers of Goodman et al. and Lin et al. to demonstrate that the prior art has described the enhancement of the expression of RNA polymerase in *E. coli* and an increase in transcription levels for *c-myc* promoter gene in eukaryotic cells, respectively after exposure to magnetic fields that are well within the range of the magnetic fields used in the presently claimed invention. Applicant further argues that due to the similarity in operational parameters with those described in the Goodman and Lin papers, one skilled in the art would be able to practice the claimed invention without undue experimentation and routinely. Applicant further argues that Applicant has provided working examples demonstrating the effect of described SELF processes on three different cell lines. Accordingly, the presently claimed invention is fully enabled. Applicant's arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, neither the Goodman paper nor the Lin paper concerns with the modification of a p53 gene using SELF non-thermal fields. Goodman et al. simply demonstrated an enhanced synthesis of a bacterial protein in a cell-free transcription/translation system following exposure to 72 Hz sinusoidal fields in the range 0.07-1.1 mT; while Lin et al. showed that a specific region of the c-myc promoter is responsive to electric and magnetic fields. Moreover, neither Goodman nor Lin

showed that the electric and magnetic fields actually modify the bacterial genes and the *c-myc* gene tested. Goodman et al. stated "Although these data show enhanced synthesis of a protein in a cell-free system, they do not directly address the question whether the increase occurs as a result of enhanced transcription, translation or both.....Data from this lab (not shown) support the conclusion that weak field exposure increases RNA levels; whether this is due to enhanced synthesis or decreased degradation of RNA remains an open question" (page 111, col. 1, first paragraph).

Secondly, as already noted above the decrease in the level of p53 antigen that is detected by the immunohistochemical approach in tumor cells exposed to SELF non-thermal fields is not deemed to correlate with any modification of the mutant p53 gene present in tumor cells. This is because the decrease level of a p53 expression can be caused by a host of factors (e.g., numerous factors involved transcriptional initiation, elongation, mRNA stability) that have nothing to do with the modification of the p53 gene itself. Moreover, the observed lower p53 expression level in cancer cells exposed to SELF non-thermal fields is apparently caused by an enhanced apoptotic rate and/or toxicity in the treated cancer cells (see Tables 3 & 4 for a significantly higher apoptosis, and lower proliferative index and mitosis in treated cancer cells), and not by the modification in the mutant p53 gene. At best, Applicant has shown that SELF non-thermal fields induced apoptosis in cancer cells in both *in vitro* and *in vivo*, and not the modification of any p53 gene in any shape or form.

Accordingly, In light of the totality of the prior art at the effective filing date of the present application, and given the lack of sufficient guidance provided by the instant

specification, it would have required undue experimentation for a skilled artisan on how to make and use the method as claimed.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Quang Nguyen, Ph.D.

PRIMARY EXAMINER